

HLA-DQ Allele Combinations and Antibody Profiles in Children with Type 1 Diabetes: A Retrospective Study

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INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease where T cells gradually destroy pancreatic beta cells. The strongest genetic factors influencing T1D susceptibility are HLA-DQ haplotypes, which affect the variety of autoantigens presented to T cells. Islet autoantibodies, such as insulin (IAA), glutamic acid decarboxylase (GAD), islet antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A), are established markers of autoimmune activity, with varying prevalence and clinical implications among patients.

OBJECTIVES

To assess the relationship between HLA-DQ single alleles and pairs of allele combinations with the presence of four islet autoantibodies at the diagnosis of T1D in a pediatric cohort, we employed a data-driven variable selection approach followed by robust regression modeling.

METHODS

A retrospective study was conducted involving 180 children with Type 1 Diabetes (T1D) recruited at Buzzi Hospital between October 2014 and March 2025. All patients under-

went HLA-DQ genotyping, and individual allele carrier status was coded as binary variables. From the cohort, all pairwise allele combinations with sufficient frequency were identified and tested alongside single alleles as potential predictors. Variable selection for each autoantibody outcome was performed independently using optimized Random Forest models, with hyperparameter tuning to minimize out-of-bag error. The top predictors identified were subsequently entered into Poisson regression models with robust sandwich variance estimation, yielding prevalence Risk Ratios (RR) and valid confidence intervals. All p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure, applied globally across all tests.

RESULTS

Preliminary results indicate that specific alleles, namely DQ8 and DQ7, are independently associated with positivity for IA-2A after applying false discovery rate (FDR) correction. The relative risks (RR) for DQ8 and DQ7 are 1.48 (95% confidence interval [CI] 1.13–1.96, $p = 0.023$) and 1.49 (95% CI 1.12–1.97, $p = 0.023$), respectively. However, no single allele was found to be significant for GADA, ZnT8A, or IAA positivity after adjustment. Among allele pairs with sufficient frequency, the combination of DQ5 and DQ6 showed a significant association with IAA positivity, yielding an RR of 3.22

(95% CI 1.37–7.55, $p = 0.011$). Additionally, the allele pairs DQ8×DQ7 and DQ2×DQ7 were associated with IA-2A positivity, both showing an RR of 1.46 (95% CI 1.08–1.99, $p = 0.021$). No allele pairs reached significance for GADA or ZnT8A positivity after FDR correction.

CONCLUSIONS

This study shows that HLA-DQ alleles influence islet autoantibody profiles in children with T1D, both individually and in combination. Distinct signatures emerge across different autoantibody specificities. DQ8 and DQ7 are identified as independent predictors of IA-2A positivity, while combinations of alleles reveal additional associations that single alleles do not capture. Notably, the combination of DQ5 and DQ6 is linked to insulin autoantibodies (IAA), and the combination of DQ8 and DQ7 is associated with IA-2A. These findings support a combinatorial model of how HLA-DQ influences autoimmune targeting and provide a foundation for further validation in larger prospective studies.